The Advent of Non-Thermal Non-Tumescent Techniques for Treatment of Varicose Vein

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Keywords: varicose veins; mechanochemical ablation; cyanoacrylate glue

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Abstract

Varicose veins are common and their management has undergone a number of changes over the years. Surgery has been the traditional treatment option, but towards the twenty-first century, new endovenous thermal ablation techniques, namely, radiofrequency ablation and endovenous laser ablation, were introduced which have revolutionised the way varicose veins are treated. These minimally invasive techniques are associated with earlier return to normal activity and less pain as well as enabling procedures to be carried out as day cases. They are, however, also known to cause a number of side-effects and involve infiltration of tumescent fluid which can cause discomfort. Non-thermal, non-tumescent (NTNT) methods are believed to be the answer to these unwelcome effects. Ultrasound-guided foam sclerotherapy is one such NTNT and, despite a possible lower occlusion, has been shown to improve the quality of life of patients. The early results of two recently launched NTNT, mechanochemical ablation and cyanoacrylate glue, are promising and are discussed.

Keywords: varicose veins; mechanochemical ablation; cyanoacrylate glue

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The management of varicose veins has changed drastically over recent years, but the ideal treatment remains elusive. Traditionally, varicose veins have been treated with surgical ligation and stripping under general anaesthetic, but, over the past decade, minimally invasive techniques and local anaesthesia have become increasingly popular and indeed preferred[1]. These have also been shown to be associated with less peri-procedural pain and an earlier return to normal function[1]. These endovenous techniques are cost-effective, especially when performed in an outpatient or 'office-based' setting[2].

The National Institute of Clinical Excellence (NICE) guidelines published in July 2013 recommended the use of endovenous thermal ablation techniques, namely radiofrequency ablation (RFA) or endovenous later ablation (EVLA), as first line treatment for truncal reflux[3, 4]. Occlusion rates of greater than 90% have been demonstrated in studies looking at these two methods at up to 2 years of follow-up [1, 5-7].

However, because they make use of thermal energy to denature the venous wall, they have the potential of causing pain, skin burns, skin pigmentation, nerve damage and, even, arteriovenous fistula formation[8, 9]. To minimise these possible complications, tumescent anaesthesia has to be infiltrated around the vein to be treated. This, in turn, can be a source of discomfort to patients.

Non-thermal, non-tumescent (NTNT) methods, hence, seem to be able to provide an alternative solution to the problems raised by these thermal techniques. In this review, we will be discussing the various NTNT techniques available nowadays, including their various qualities.

Foam Sclerotherapy: The Original NTNT

Sclerosing solutions react with endothelium damaging it (endosclerosis) and causing fibrosis (endofibrosis) of the vessel lumen[10]. Orbach (1944) initially described the combination of air and sclerosing drug to treat varicose veins: the so-called 'air block' technique[11]. This technique, with a higher air to liquid ratio, was effective for the treatment of smaller veins, but was not suitable for larger ones as the air would position itself on the upper side of the vein, thereby preventing contact with endothelium. But it was not until the 1990s that foam sclerotherapy enjoyed a period of renaissance, when new methods of transforming liquid sclerosants into foam were described[12]. Sclerosing agents used as foam displace venous blood and increase endothelial contact, thereby, augmenting their sclerosing power[13]. One of the most widely used technique to produce foam is the Tessari method, which requires two syringes and a three-way tap and enables the production of a stable and compact foam[13]. The optimal formulation was found to be one part liquid sclerosant to four parts air[13]. Evolution of the technique have continued, with the introduction of ultrasound guidance (ultrasound guided foam sclerotherapy) or catheter directed foam sclerotherapy for the treatment of truncal veins[14-16]. Two of the most common sclerosing solutions available are sodium tetradecylsulphate (STS) and polidocanol (POL).

Yamaki et al. (2004) demonstrated the superiority of foam over liquid sclerosants in a comparative non-randomised study of ultrasound-guided sclerotherapy using either foam or liquid[17]. Sixty-two women, with mean age of 54.6 years, were recruited and received polidocanol either as foam or liquid to treat great saphenous vein (GSV) insufficiency. At 12 months follow-up, approximately 68% of patients receiving foam sclerotherapy had evidence of complete occlusion compared to 17.5% of those in the liquid therapy group ($p<0.0001$)[17]. Despite both groups having similar characteristics, the study is limited by a lack of randomisation as well as unclear criteria used in recruitment.

Consecutive patients attending for varicose vein treatment were offered ultrasound-guided foam sclerotherapy (UGFS) to refluxing truncal veins (saphenous and non-saphenous)[18]. In total, 181 patients were enrolled and reviewed within 6 weeks of treatment. Approximately 60.0% were females with a median age of 52 years. The occlusion rate was 74% after the first intervention and a further 15% after two interventions[18]. Common complications included phlebitis and pigmentation.

Coleridge-Smith (2006) evaluated his own series of 808 patients undergoing UGFS for incompetent truncal veins and, in the 459 patients attending follow-up at 6 months or greater, demonstrated an occlusion rate of 88% for the GSV and 82% for the short saphenous vein (SSV)[19]. Three interventions (each separated by 2 weeks) were required to achieve an occlusion rate of 99% of the unilateral varices.

When compared to other treatment modalities, foam sclerotherapy proved to be less effective. Rasmussen et al. (2011) conducted a randomised controlled trial to compare endovenous laser therapy (EVLT), radiofrequency ablation (RFA), UGFS and surgical stripping in patients with evidence of GSV incompetence[1]. Five hundred patients were recruited and the follow-up period was for 1 year. The primary outcome measure was treatment failure, which was defined as an open part of the treated vein segment measuring more than 10cm in length. The clinical, quality of life and radiological change after intervention was also recorded. Baseline characteristics for all four groups did not differ. At 1 year follow-up, there were significantly more cases of treatment failures in the UGFS group (16.3%) compared to the other three groups (less than 6%) ($p<0.001$)[1]. Patients who were treated with either UGFS or RFA reported lower pain scores and returned to their normal activities earlier compared to those receiving EVLT or surgery ($p<0.001$). All groups improved similarly in both clinical and quality of life scores. UGFS was also found to be the cheapest treatment method, especially when the cost of being off from work was taken into account.

Lower occlusions rates were again reported in the MAGNA trial. This was a randomised controlled trial comparing EVLT, UGFS and surgery in 223 patients (240 legs)[20]. The primary outcome measure was anatomic success on duplex ultrasound examination. At the 1-year follow-up, both EVLT and surgery had comparable occlusion rates (88.5% and 88.2%, respectively). The corresponding occlusion rate for UGFS was 72.7% ($p<0.02$). All three groups also demonstrated similar improvement in the quality of life scores (CIVIQ and EQ-5D).

The longest data to date following UGFS has been reported by Darvall et al. (2014)[21]. They described the patient-reported outcomes 5-8 year following treatment with UGFS. Out of the initial 351 patients (479 limbs) treated, 285 (81.2%) attended follow-up a minimum of 5 years later. Using a Kaplan-Meier plot, they estimated the proportion of their cohort requiring retreatment at 5 years to be 15.3%. There was also significant improvement noted in the Aberdeen Varicose Vein Symptom Severity score (AVSS), similar to that observed at earlier follow-ups. The physical component of the Short Form12 (SF-12®) was also found to have improved compared to pre-treatment values. The mental component of SF-12® was, however, similar to baseline levels. Between 62.7% and 81.0% reported exceeded or met expectations with respect to social, work or leisure activities. Eighty-two percent of patients were highly satisfied (giving a score of 8 to 10) and more than 90% would recommend the

treatment to their family and friends. The same group also demonstrated that UGFS are less painful, improve the quality of life of patients and lead to earlier return to work[22-24].

Complications associated with UGFS include phlebitis, skin pigmentation, thromboembolism (pulmonary embolus or deep vein thrombosis) as well as neurological symptoms such as migraines, transient ischaemic attacks or visual disturbances[18, 25]. The occurrence of neurological symptoms have been attributed to the presence of a patent foremen ovale (PFO), a common finding in the population (20-30%)[25].[18, 26]

Newer NTNT methods have recently appeared on the market and these are being promoted as offering the potential of higher occlusion rates, while maintaining improved quality of life and earlier return to activities, but without the side-effects of endothermal ablation.

Mechanochemical Ablation

A new device, the ClariVein® mechanochemical ablation (MOCA) device (Vascular Insights, Madison, CT, USA), has been introduced which avoids the use of heat and tumescent infiltration. It combines an endovenous mechanical method using a rotating wire with simultaneous injection of liquid sclerosant[27]. The wire rotates at 3500 rotations per minute, injuring the venous intima while the sclerosant is infused through an opening close to the catheter tip[27].

Animal Studies

Tal et al. (2014) tested the MOCA device on 11 male goats (12 veins included) and analysed the histological samples obtained from this caprine model[28]. Four different treatments were examined: group 1 - the ClariVein® catheter and 1.5% Sodium tetradecyl sulphate (STS) (MOCA procedure) (five veins); group 2 - ClariVein® and 0.9% saline (one vein); group 3 - 5mL injection of 1.5% STS (five veins); and, group 4 - 5mL injection of 0.9% saline (one vein). The lateral saphenous vein was selected and duplex ultrasound examinations were carried out pre-operatively and on days 14, 28, 56 and 84 to assess the degree of occlusion. At day 84, all animals were euthanised and underwent gross necropsy[28]. All the veins receiving the MOCA procedure (group 1) demonstrated complete or near complete occlusion on ultrasound assessments at 84 days, while the veins in the other treatment groups were still patent at the end of the study, thereby indicating the superiority of the ClariVein® catheter and sclerosant to produce vein occlusion and fibrosis rather than only using liquid sclerosant. Comparison of the saline groups (groups 2 and 4) showed more subintimal impingement and medial fibrosis in group 2 than in group 4.

No adventitial fibrosis was demonstrated, however, and veins from both groups remained patent at the end of the study.

One limitation of the study is that the number of veins treated in each group is not equivalent and the question remains as to whether some of the changes noted could have been improved with inclusion of a larger number of veins. This study, in any case, illustrates the superiority of the MOCA procedure in achieving venous occlusion compared to using either the ClariVein® catheter alone or liquid sclerosant on its own.

Human Trials

In order to determine the safety and efficacy of the ClariVein® device, Elias and Raines (2012) recruited 29 patients with great saphenous vein (GSV) reflux and followed them at 4 different time points[27]. A majority of the patients were females (60%) and the average age of the population was 54.3 years (range: 31 to 90 years). The baseline Venous Clinical Severity Score (VCSS) was 4.5 with the clinical CEAP (Clinical-Etiological-Anatomical-Pathophysiological) between 2 and 4. The average treatment length was 37.5cm and the average diameter of the treated veins was 8.1mm. No patients complained of pain during the ablative procedure. There were no incidences of deep vein thrombosis (DVT), nerve or skin injury. The average follow-up period was 260 days. There was one case (1 out of 30) of recanalization giving a primary closure rate of 96.7% at 260 days[27]. The authors, therefore, concluded that the new ClariVein® device was safe and appeared to be effective in the treatment of venous reflux[27]. However, most of the patients recruited had CEAP stage 2 disease (77%) and there were three occurrences of ecchymoses. The authors postulate that this might be secondary to the rotating wire catching on a side branch or valve cusp.

About the same time, van Eekeren et al. conducted a similar study in the Netherlands to assess the applicability and safety of MOCA. Twenty-five patients with GSV reflux were recruited (30 limbs), undergoing mechanochemical ablation at two centres[29]. Most of the patients were women (72%) and the mean age of the population was 52 years. The CEAP classification ranged from C2 to C4 and the mean VCSS score was 3.3. The mean duration of the procedure was 20 minutes and the treated veins were on average 40cm in length and 6.1mm diameter at the sapheno-femoral junction. The median maximal pain score was 4 (interquartile range (IQR) 3-6) on a 10-point scale, while the mean maximum pain measured on day 1 post-procedure was 9mm on a 100mm visual analogue scale (VAS)[29]. There were no major adverse events and the minor complications included 9 cases of local ecchymosis at the puncture site and 4 of phlebitis. The GSV was completely obliterated in 87% of cases (26 out of 30 legs treated) at the 6 weeks follow-up.

Patient satisfaction was 8.5 (IQR 8-9) on a 10-point scale and the median VCSS decreased significantly from 3 to 1 (P<0.001)[29].

The effect of MOCA on the small saphenous vein (SSV) has been studied by the same group. The SSV accounts for approximately 15% of lower limb truncal venous incompetence[30]. Fifty patients with SSV incompetence were enrolled and received MOCA treatment to their incompetent SSV with 1.5% Polidocanol as sclerosant[30]. The median pain score using a VAS was 2cm (IQR 2-4 cm) and the median patient satisfaction was 8 (IQR 8-9). No major complications were recorded, including no evidence of nerve injury and no DVT. Minor complications were noted, mainly localised ecchymosis and induration and transient superficial thrombophlebitis in 14%. The occlusion rate was 100% (50 out of 50 limbs treated) and 94% (44 out of 47 legs treated) at the 6 weeks and 1 year follow-up, respectively. However, it is to be noted that different concentrations of the sclerosant were used to treat the proximal section, with 1.5% Polidocanol for the first 15 patients, but 2ml of 2% Polidocanol in the subsequent 35 patients (followed by 1.5% for the remainder of the vein). There were two occurrences of recanalisation in patients treated with the lower concentration, compared to 1 out of those who received 2% Polidocanol.

The same group again evaluated the 1-year results of MOCA in patients with GSV insufficiency[31]. Consecutive patients with GSV insufficiency were included in the study. Ninety-two patients (106 limbs) were recruited. The mean age was 52 years with 67% of the cohort being females. MOCA was performed on 105 legs and the median post-procedural pain using a 0-100mm VAS during the first 14 days after treatment was 7.4mm. No major complications were observed, although there were incidences of thrombophlebitis, induration, localised haematoma and mild hyperpigmentation at the puncture site. The occlusion rate immediately post-procedure, at 6 months and at 1 year was 100%, 93.2% (96 of 103 limbs treated) and 88.2% (90 of 102), respectively[31]. The mean VCSS score improved significantly at the 6 months and 1 year follow-up (p<0.001). Compared to baseline, the QoL improved significantly with a mean AVVQ score of 6.6 at 6 months (p<0.001) and 2.4 at year 1 (p<0.001).

There have been few studies comparing MOCA to endothermal ablation. One of these studies comprised of 68 consecutive patients treated for symptomatic unilateral GSV reflux and their post-operative pain score as well as early quality of life was assessed[32]. Thirty-four patients were assigned to either MOCA or radiofrequency ablation (RFA). There were 25 males and 43 females, with a mean age of 58 ± 17 years. There were no significant differences in the baseline patient characteristics. The mean procedural pain during treatment was similar between the two groups (p=0.16). Patients receiving MOCA reported less pain compared to RFA over the first three days (6.2mm v/s 20.5mm; p=0.004) and during the first 14 days after treatment

(4.8mm v/s 18.6mm; p<0.001)[32]. They also required less analgesia compared to the RFA group. Patients in both groups who developed post-operative thrombophlebitis and induration had higher pain scores. Treatment time was significantly shorter in the MOCA group (p=0.02). At 6 weeks, the median VCSS score improved significantly in both groups (p<0.001). Quality of life assessment showed that the AVVQ score improved in both the MOCA (p=0.006) and RFA (p=0.002)[32]. Time to return to normal activities and work was also found to be significantly shorter in the MOCA group. The authors, thus, concluded that post-operative pain is significantly lower after MOCA compared to RFA and the former was associated with a faster return to normal activities and work. This is the first study which has provided direct evidence of the lesser discomfort following varicose vein ablation and earlier return to activities in patients receiving MOCA. But, this was a non-randomised trial and the criteria used for patient selection is not clear. Moreover, the procedural pain score was no different in the two groups, but the authors allude to the fact that their sample size was too small to detect a difference and suggested carrying out a randomised trial.

In our unit, we are conducting a multicentre randomised clinical trial (RCT) comparing MOCA to RFA and looking at the intra-procedural pain scores and improvement in quality of life at 1 and 6 months[33]. One hundred and nineteen patients had been randomised thus far, with 60 of them from the MOCA group. The patients' baseline characteristics were similar and there was no significant differences between the CEAP class of each group. These early results demonstrate significantly lower maximum (19.3mm versus 34.5mm) and average VAS pain score (13.4mm versus 24.2mm) in the MOCA group compared to the RFA group (p<0.001 and p<0.001, respectively). Seventy-eight patients (66%) attended their one month follow-up appointment. Both clinical and quality of life (QoL) scores improved by then. However, there was no significant difference in the time taken to return to normal activities and work. The complete/proximal occlusion rates at one month was 92% in both groups (P=0.89). The trial is still in its follow-up phase at present.

The MARADONA trial (Mechanochemical endovenous Ablation versus RADiOfrequeNcy Ablation in the treatment of primary great saphenous vein incompetence) has been designed to directly compare the anatomical and clinical success rate at one year compared to RFA and is hoping to recruit 230 patients in each group (460 patients in total)[34]. Patients will then be followed up for 5 years, giving excellent long term data. The results of this are eagerly anticipated and expected in 2020.

Cyanoacrylate Glue

Another tumescentless method recently introduced is the Sapheon Venaseal Closure System (Sapheon Inc., Santa Rosa, Calif, USA) which makes use of cyanoacrylate glue to treat venous incompetence.

What is glue?

The glue used in this tumescentless method is n-butyl cyanoacrylate (n-BCA), which was initially introduced in medical practice approximately 40 years ago[35]. The first cyanoacrylate adhesive used at the time had low tensile strength and was associated with both acute and chronic inflammation[35].

N-butyl cyanoacrylate is an adhesive liquid monomeric agent which quickly polymerises and becomes solid when it comes into contact with a solution containing anions (e.g., with the hydroxyl groups in blood)[36]. This subsequently leads to occlusion, marked inflammatory endothelial response, and, ultimately fibrosis[36]. Further development of the material with the addition of plasticisers and stabilisers have improved its flexibility and reduced its toxicity[35].

This has resulted in cyanoacrylate glue being used more widely, for example, in ophthalmic surgery, cosmetic procedures, dental applications, tissue adhesion and haemostasis of acute bleeding such as endoscopic sclerotherapy of gastric variceal bleeding with high safety profiles reported in patients followed up for 10 years[37]. They have also been used intravascularly in treating type I and II endoleaks of abdominal aortic aneurysm repair procedure, varicocoeles, pelvic congestion syndrome and arterio-venous malformations (AVM)[37].

Animal Studies

Kailasnath and Chaloupka (2002) developed a bench top testing apparatus that permits direct measurement of evolving binding forces that develop during polymerization of CA[38]. They compared the rate of polymerisation of CA using a plastic model vessel and a tissue model (common carotid artery of a swine). They found that there were three distinct stages of polymerization. The initial phase (phase I) demonstrated a linear rate of increasing tensile forces lasting less than 10 seconds followed by phase II which had a more constant tensile force (lasting up to 1 minute). Polymerisation was, however, not achieved in either phases. A final step (phase III) started at the end of the second phase and was characterised by an exponential rise in the tensile forces which lead to complete polymerisation[38]. The rate of polymerisation and strength of the binding forces formed were variable and dependent on type and formulation of CA used[37, 38].

The first experiment looking at using CA adhesive as vein closure method in an animal model used the superficial epigastric veins (SEVs) of two swines[39]. The SEVs empty into the abdominal rectus vein (ARV) at the costal margin. The purpose of the

experiment was to assess the feasibility of the proposed method as well as evaluating its safety and effect on the vein wall. With the swines under general anaesthetic, the right and left SEVs were cannulated followed by insertion of the CA adhesive delivery catheter (Sapheon, Santa Rosa, California). This venous closure system also incorporates a 3cc (cubic centimetre) syringe, a dispenser tip and a dispenser gun (Sapheon)[39].

The method of treatment used was as follows. The catheter tip was positioned 2cm distal to the SEV-ARV junction. Pressure was then applied with the ultrasound transducer just cephalad to the catheter tip. Using a slow deliberate trigger pull of 3-second duration, 0.16mL of CA was delivered to the target vein. The delivery system (sheath plus catheter) was immediately pulled back 3cm after this initial injection and transverse compression applied for 30 seconds to allow interaction between CA and the vein wall. This process was repeated every 3cm until the vein was treated.

Four SEVs were treated in total and the two swines were sacrificed at day 60 post-treatment[39]. The SEVs were harvested and sections were studied macro- and microscopically. Explanted segments from the caudad, middle and cephalad areas were completely occluded with no patent segments. On histology, fibrous tissue and inflammatory cells were present, with 1 of the 3 examined sections exhibiting fibrotic projections which caused occlusion of nearly the entire lumen. The wall was segmentally thickened by fibrous tissue and the lumen was dilated by an abundant clear space containing moderate amounts of debris and coalescing, tree-like bands of microphages and spindle cells. The clear space appeared surrounded by multinucleated giant cells, which were presumed to be reacting toward foreign material. Spindle cells with dense eosinophilic matrix replaced the tunica intima and disrupted the tunica media. Additionally, the wall was disrupted by numerous aggregates of histiocytes and lymphocytes with lymphoid follicles. Also, a dark-coloured bulge (entrapped blood) in the vein was observed, though not visible on the skin. The changes observed in the treated veins are consistent with chronic foreign-body-type inflammatory response. Unwanted migration of CA was not found, nor was recanalisation present in any of the treated veins. Evaluation of control segments lacked any significant histologic changes[39].

Human Trials

The first clinical trial of using cyanoacrylate adhesive for the treatment of varicose veins recruited 38 patients with great saphenous vein incompetence in a prospective non-randomised study[40]. Consecutive patients were enrolled and followed up at 48 hours and 1, 3, 6 and 12 months after their intervention with a clinical examination and a duplex ultrasound scan. Complete occlusion of the treated segment was considered as treatment success. A disposable Sapheon Closure System (SCS) was

used which included a delivery catheter with hydrophobic properties to prevent CA-mediated adhesion to the vein wall[40]. The catheter was removed after venous closure has been confirmed and a single adhesive bandage was applied. No additional procedures were carried out and no compression stockings or bandages were applied. Approximately three quarters of the patients were females with a median age of 51 years (range: 26-77 years)[40]. The mean GSV diameter at the SFJ was 8.0 ± 2.2mm and the mean length of vein treated was 33.8 ± 9.1 cm. The mean volume of CA glue used was 1.3mL (range: 0.6-2.3mL). All the veins treated were completely occluded at the 48 hour follow-up. By the 12 months follow up, 3 patients had developed recanalisations of GSV, giving a complete occlusion rate of 92.1%[40]. Seven patients developed post-operative thrombophlebitis, 1 patient developed cellulitis and one patient had hyperpigmentation at 12 month due to the treated vein being very close to the skin. In addition, 8 patients had evidence of thread-like thrombus extension across the SFJ into the common femoral vein (CFV) at the 48-hour follow-up (protruding a length of 12.6 ± 9.9mm). All thrombus extensions had resolved without any anticoagulation by the 6 months follow-up. The VCSS scores showed improvement from 6.1 ± 2.7 at baseline to 1.5 ± 1.4 at 12 months ($p<0.0001$). This study set out to determine the feasibility of using CA in the treatment of saphenous vein incompetence. It also demonstrated an occlusion rate comparable to those of endothermal ablation methods in use. Patients were seen again at the 12 and 24 months period[41]. The occlusion rate at the 24 months mark using a life-table analysis was 92%[41]. The VCSS score at 24 months was lower than baseline, although it was still higher than the score at 6 months. These results demonstrate that CA is potentially an alternative to the endothermal methods, especially as no tumescent or compression is needed. Two of the authors had connections with the funding company, Sapheon Inc., and with consulting firms with an interest in the device.

Proebstle and colleagues (2013) undertook a prospective, multi-centre clinical trial of endovenous CA embolisation of refluxing GSVs in seven centres across Europe[42]. Symptomatic patients with GSV incompetence confirmed on duplex ultrasound were recruited and treated with CA, starting at 5cm distal to the SFJ. No post-procedure compression was used. No adjunctive treatment or reintervention was undertaken for three months after the intervention. Clinical and quality of life assessments were carried out at baseline and patients were followed up at 48 hours and at 1, 3, 5 and 12 months initially. Seventy patients were enrolled in total with 79% of them being females. The mean age was 48.4 years (range: 22-72 years). The mean diameter of the GSV at the SFJ was 7.8mm and the mean length was 37.6cm. The mean treatment time was 18.6 minutes (range: 8-74 minutes). Using a life-table method, the complete occlusion rate was 92.9% at the 12 months follow-up point[42]. The

patients' clinical and QoL scores were significantly improved. The most common adverse events were phlebitic reaction, occurring in 8 limbs. A single patient had a 6mm extension of thrombus into the common femoral vein. This was successfully treated with low molecular weight heparin. Thus, this study demonstrated that CA was safe and effective in the treatment of GSV reflux and an RCT comparing the technique to endothermal methods have been advocated.

In the VeClose trial, a multicentre randomised controlled trial comparing cyanoacrylate embolisation and radiofrequency ablation for refluxing great saphenous veins, two hundred and twenty-two patients were recruited and randomised to receiving CA or RFA[43]. The primary study end-point was complete closure of the GSV and patients were followed up for 3 months. Prespecified models were used to impute missing data. Most patients were females (79%) and Caucasian (94%) with the most common CEAP clinical class being 2 and 3. The mean age was 49.0 years and 50.5 years for CA and RFA, respectively. The occlusion rate in both groups was 100% at day 3. At the 3 month point, the occlusion rates were 99% for CA and 96% for the RFA group. However, this was obtained using predictive statistical models to compensate for missing data (31/222). At 3 months VCSS, AVVQ and generic quality of life all showed significant improvement compared to baseline (3.5, $p<0.01$; 8, $p<0.01$ and 0.03, $p=0.01$, respectively). There was non-significant increased incidence of phlebitis in the CA group, with less ecchymosis at day 3 in the CA group compared to the RFA group (68% of CA group were free from ecchymosis compared to 48% from the RFA group; $p<0.01$). Venous access and mean intraprocedural pain scores for both methods were similar. Multiple imputation models showed non-inferiority with both optimistic and pessimistic models.

Conclusion

So far, the two newer NTNTs have been shown to be at least equivalent to endothermal techniques and probably superior to UGFS with respect to occlusion rates. They also appear to offer better comfort and earlier return to normal activities. Despite their undeniable promise, further randomised controlled trials with longer follow-up will hopefully be able to provide more robust evidence of their respective merits.

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